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Supplementary appendix

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Vitamin D supplementation to prevent asthma exacerbations: systematic review and meta-analysis of individual participant data

Appendix

Search Strategies

A. Medline

Cochrane Highly Sensitive Search Strategy for identifying randomized controlled trials

#1. randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]

#2. animals [mh] NOT humans [mh]

#3. #1 NOT #2

Terms specific to vitamin D

#4. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Terms specific to asthma

#5 Asthma OR bronchial hyperreactivity OR bronchial hyper-reactivity OR respiratory hypersensitivity OR reactive airway

Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with asthma

#3 AND #4 AND #5

B. RANDOMIZED

Terms for identifying randomized controlled trials

#1 ‘randomized controlled trial’/exp OR ‘single blind procedure’/exp OR ‘double blind procedure’/exp OR ’crossover procedure’/exp
#2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR ’cross over’:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEXT/1 blind*):ab,ti OR trial:ti
#3. #1 OR #2

Terms specific to vitamin D

#4. vitamin AND d OR vitamin AND d2 OR vitamin AND d3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Terms specific to asthma

#5 asthma OR (bronchus AND hyperreactivity) OR (respiratory AND tract AND allergy) OR (reactive AND airway*) OR asthma* OR (bronchial AND hyperreactivity) OR (bronchial AND 'hyper reactivity') OR (respiratory AND hypersensitivity)

Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with asthma

#3 AND #4 AND #5

C. Cochrane Central

Terms specific to vitamin D

#1. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

Terms specific to asthma

#2. Asthma OR bronchial hyperreactivity OR bronchial hyper-reactivity OR respiratory hypersensitivity OR reactive airway

Combination of terms to identify randomised controlled trials of vitamin D conducted in patients with asthma

#1 AND #2

D. Web of Science

TS =(Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol) AND TS =(Asthma OR bronchial hyperreactivity OR bronchial hyper-reactivity OR respiratory hypersensitivity OR reactive airway) AND TS =(placebo* or random* or clinical trial* or double blind* or single blind* or rct)

Results

Appendix Table 1: Asthma exacerbations requiring treatment with systemic corticosteroids by study and allocation

Study first author & year	No. participants, control arm	No. participants with ≥1 exacerbation, control arm	No. exacerbations, control arm	Duration of follow-up, control arm (participant-years)	No. participants, intervention arm	No. participants with ≥1 exacerbation, intervention arm	No. exacerbations, intervention arm	Duration of follow-up, intervention arm (participant-years)
Urashima 2010[1]	56	0	0	18.0	43	0	0	14.1
Majak 2011[2]	24	0	0	11.9	24	0	0	13.1
Castro 2014[3]	207	36	44	109.0	201	24	24	105.4
Martineau 2015[4]	125	32	51	116.7	125	26	42	117.4
Tachimoto 2016[5]	35	0	0	16.8	54	1	1	26.5
Kerley 2016[6]	22	8	13	7.0	17	5	9	5.2
Jensen 2016[7]	11	5	13	5.3	11	7	9	4.9

Appendix Table 2: Risk of Bias Assessment

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Urashima 2010[1]	✓	✓	✓	✓	✓	✓	✓
Majak 2011[2]	✓	✓	✓	✓	✓	✓	✓
Castro 2014[3]	✓	✓	✓	✓	✓	✓	✓
Martineau 2015[4]	✓	✓	✓	✓	✓	✓	✓
Tachimoto 2016[5]	✓	✓	✓	✓	✓	✓	✓
Kerley 2016[6]	✓	✓	✓	✓	?	✓	✓
Jensen 2016[7]	✓	✓	✓	✓	✓	✓	✓

✓ = low risk of bias; ? = unclear risk of bias;

Appendix Table 3: Summary of Findings Table

Summary of findings:

Vitamin D compared to placebo for prevention of asthma exacerbations requiring treatment with systemic corticosteroids

Patient or population: children and adults with predominantly mild to moderate asthma
Setting: primary and secondary care
Intervention: vitamin D_3 administered orally over study duration of 15 weeks to 1 year
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin D				
Rate ratio, exacerbations requiring systemic corticosteroids, overall.	0.43 events per person per year	0.32 events per person per year (0.24 to 0.42)	aIRR 0.74 (0.56 to 0.97)	955 (7 RCTs)	⨁⨁⨁⨁ HIGH	--
Rate ratio, exacerbations requiring systemic corticosteroids, sub-group with baseline 25(OH)D <25 nmol/L.	0.42 events per person per year	0.14 events per person per year (0.05 to 0.42)	aIRR 0.33 (0.11 to 0.98)	92 (3 RCTs)	⨁⨁⨁◯ MODERATE	Quality downgraded one level for imprecision
Rate ratio, exacerbations requiring systemic corticosteroids, sub-group with baseline 25(OH)D ≥25 nmol/L.	0.46 events per person per year	0.35 events per person per year (0.27 to 0.47)	aIRR 0.77 (0.58 to 1.03)	764 (6 RCTs)	⨁⨁⨁◯ MODERATE	Quality downgraded one level for imprecision
Proportion with ≥1 exacerbation requiring ED visit or hospitalisation or both.	58 per 1,000	28 per 1,000 (15 to 53)	aOR 0.46 (0.24 to 0.91)	955 (7 RCTs)	⨁⨁⨁⨁ HIGH	--
Proportion with ≥1 serious adverse event	46 per 1,000	40 per 1,000 (22 to 73)	aOR 0.87 (0.46 to 1.63)	955 (7 RCTs)	⨁⨁⨁◯ MODERATE	Quality downgraded one level for imprecision

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

aIRR: adjusted Incidence Rate Ratio; aOR: adjusted Odds ratio; CI: Confidence interval; RCT: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Appendix Table 4: Effect of vitamin D supplementation on rate of asthma exacerbations requiring treatment with systemic corticosteroids: individual trials listed by increasing study size

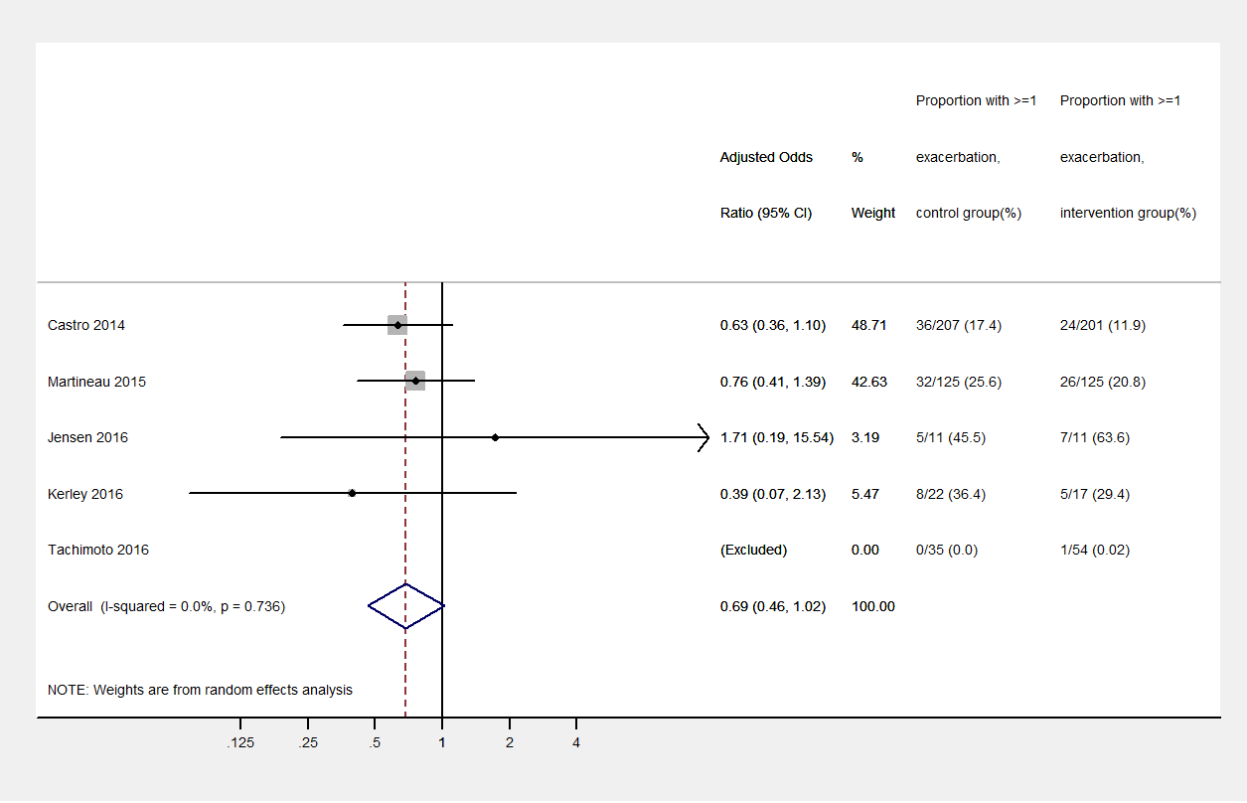
Reference	Sample size	Adjusted IRR (95% CI)
Jensen 2016 [7]	22	0.66 (0.28 to 1.58)
Kerley 2016 [6]	39	0.49 (0.18 to 1.38)
Martineau 2015 [4]	250	0.85 (0.56 to 1.28)
Castro 2014 [3]	408	0.56 (0.34 to 0.92)

Appendix Table 5: Responder analysis, one-step individual participant data meta-analysis

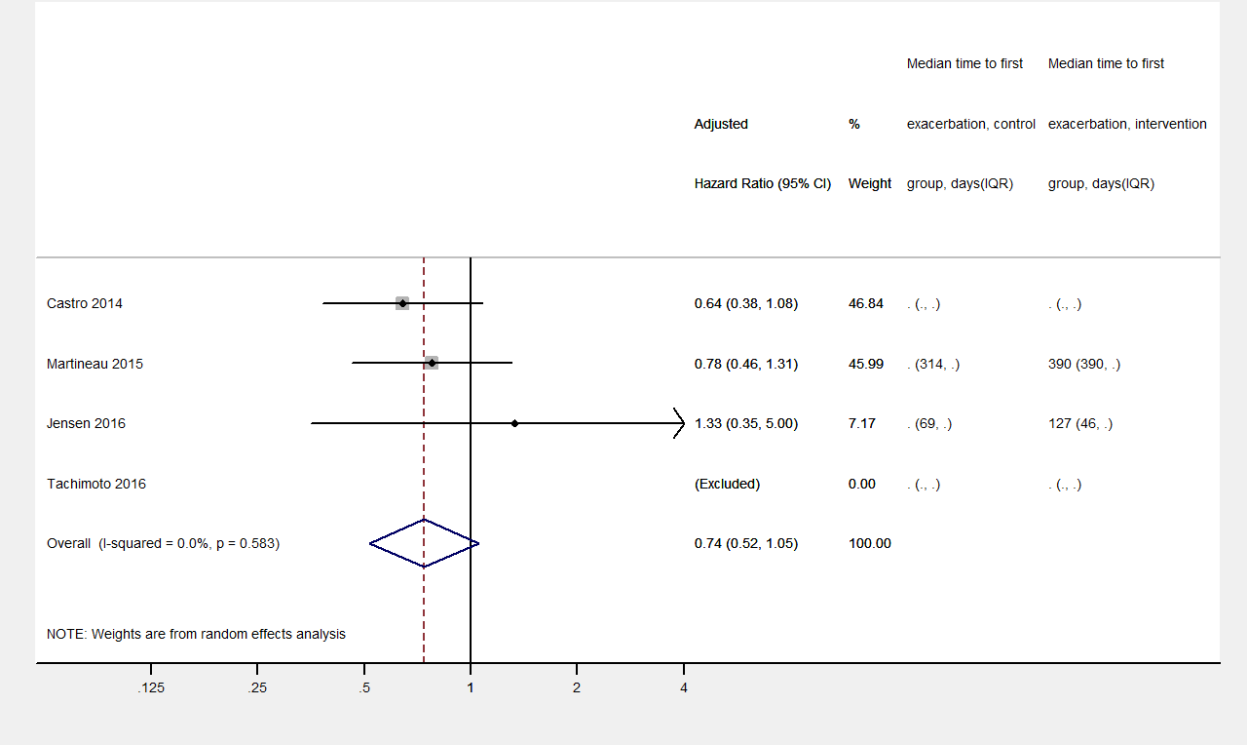
	No. participants (no. trials)	**Rate of asthma exacerbations requiring systemic corticosteroids per participant-year**	**Adjusted incidence rate ratio (95% CI)[1]**	**P value**
Intervention, end-study 25(OH)D < 75 nmol/L	131 (6)	35/100.5 (0.35)	1.00 (ref)	0.60
Intervention, end-study 25(OH)D ≥75 nmol/L	253 (6)	44/150.4 (0.29)	0.88 (0.53 to 1.44)	
	No. participants (no. trials)	**Proportion with ≥1 asthma exacerbation requiring systemic corticosteroids (%)**	**Adjusted odds ratio (95% CI)[2]**	**P value**
Intervention, end-study 25(OH)D < 75 nmol/L	131 (6)	23/131 (17.6)	1.00 (ref)	0.68
Intervention, end-study 25(OH)D ≥ 75 nmol/L	253 (6)	34/253 (13.4)	0.87 (0.44 to 1.71)	
	No. participants (no. trials)	**Median time to first asthma exacerbation requiring systemic corticosteroids, days (IQR)**	**Adjusted hazard ratio (95% CI)[1]**	**P value**
Intervention, end-study 25(OH)D < 75 nmol/L	118 (4)	-- (370 to --)[3]	1.00 (ref)	0.61
Intervention, end-study 25(OH)D ≥ 75 nmol/L	224 (4)	-- (318 to --)[3]	0.85 (0.46 to 1.59)	

1, adjusted for age and sex. 2, adjusted for age, sex and duration of participant follow-up. 3, medians and 75th centiles for time to first exacerbation requiring treatment with systemic corticosteroids in these groups cannot be defined. CI, confidence interval; IQR, inter-quartile range.

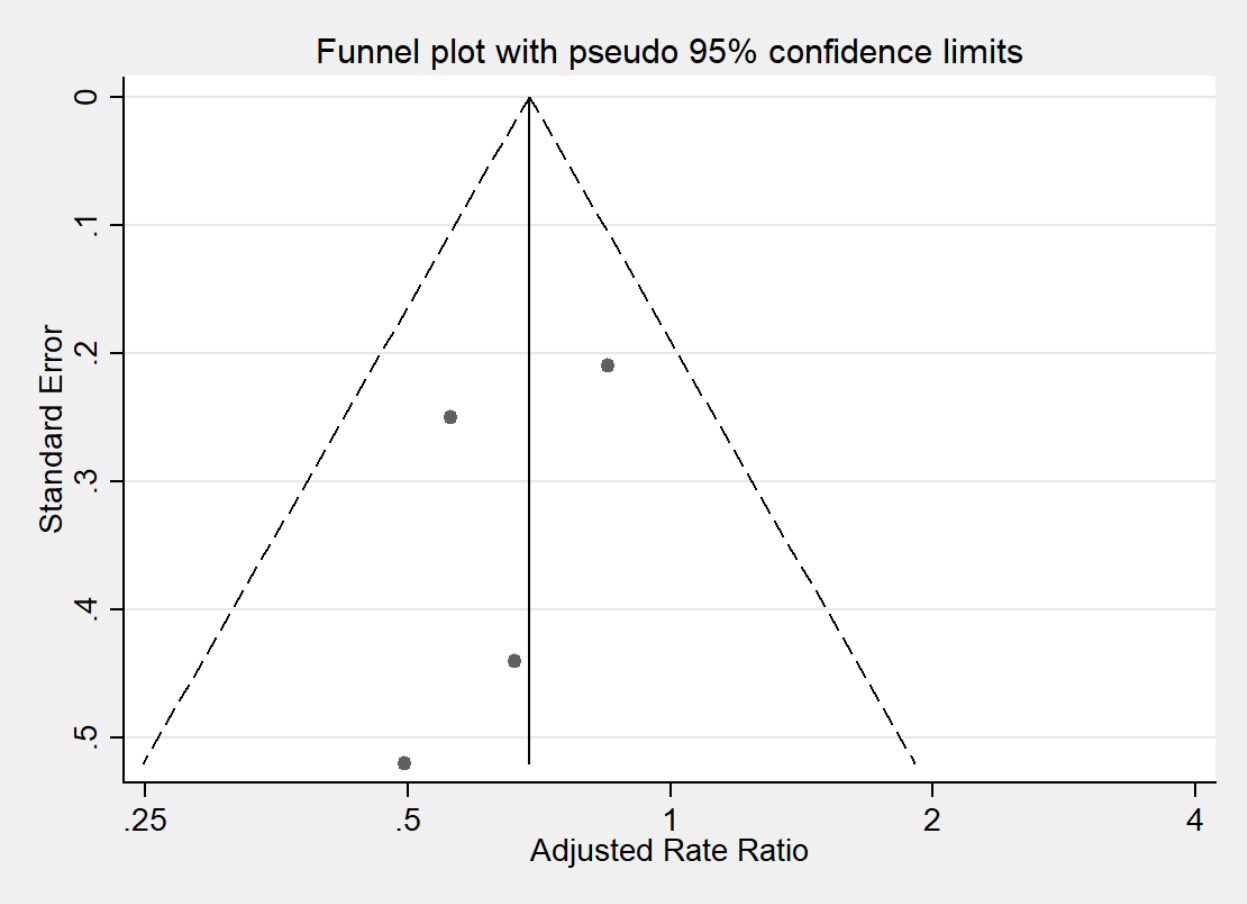
Appendix Figure 1: Two-step individual participant data meta-analysis, proportion of participants experiencing at least one asthma exacerbation requiring treatment with systemic corticosteroids



Appendix Figure 2: Two-step individual participant data meta-analysis, time to first asthma exacerbation requiring treatment with systemic corticosteroids



Appendix Figure 3: Funnel plot for individual patient data meta-analysis of rate of asthma exacerbations requiring treatment with systemic corticosteroids.



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